REMARKS/ARGUMENTS

Claims 103, 105-113, 118, 120-127 and 132-138 are pending and under consideration. No amendments have been made. The claims are reproduced for ease of references. Lack of comment on any of the Examiner's remarks should not be construed as acquiescence therewith.

35 USC § 103

Claims 103, 108, 109, 112, 113, 118, 123, 124, 127, and 132 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 5,262,332 ("Selkoe"), Solomon, *Proc Natl Acad Sci* (1996) 93:452-455 ("Solomon"), WO 97/21728 ("Nordstedt"), and U.S. Patent No. 5,773,007 ("Penney"). The Examiner cites Selkoe for discussing using antibodies to Aβ for *diagnosis* of Alzheimer's disease (Selkoe at abstract; column 2, lines 36-53), and cites Solomon for describing antibodies that bind to aggregating epitopes of Aβ. The Examiner acknowledges that Selkoe and Solomon did not explicitly identify the Aβ16-23 as an immunogenic fragment, and that Solomon did not explicitly teach administration of antibodies to patients. The Examiner cites Penney for disclosing carrier molecules, and cites Nordstedt for disclosing that the sequence "KLVFF," which corresponds to Aβ residues 16-20, is required for the polymerization or aggregation of Aβ protein. The Examiner acknowledges that Nordstedt does not explicitly teach antibodies that bind to Aβ16-20. However, the Examiner asserts that Solomon and Nordstedt taken together guide the artisan to select antibodies against Aβ16-23 for the treatment of Alzheimer's, because Solomon reports antibodies against aggregating epitopes should be used and Nordstedt reports that Aβ16-20 constitutes such an aggregating epitope. This rejection is traversed for the reasons discussed below.

It is respectfully submitted that the office action has not taken into account that the alleged case of obviousness would require change of the principle of operation of the Nordstedt reference and render it unsatisfactory for its intended purpose. If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). If the proposed modification would render the prior art invention being modified unsatisfactory for its

intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Here, Nordstedt proposes that Aβ16-20 peptide inhibits formation of amyloid fibrils by binding to Aβ, not as a result of generating antibodies to Aβ. Conjugating such a fragment to a carrier to help induce antibodies would have been counterproductive to Nordstedt's principle of operation because the extra size of the carrier would inhibit delivery of the fragment to amyloid deposits in the brain and because the presence of antibodies would tend to reduce the concentration of the intended therapeutic agent, namely the fragment. In fact, Nordstedt teaches that future effort should be directed to development of smaller organic molecules to serve as analogs of Aβ16-20 (see last paragraph) rather than larger peptides. Increasing the size of peptides would have been expected to reduce if not eliminate their ability to reach amyloid deposits in the brain. Thus, the proposed modification both changes the principle of operation of Nordstedt's peptide and renders it unsuitable for its intended purpose.

The Examiner says that it does not matter that other art may not point to the 16-20 region as being the key region of Aβ to focus on therapeutic treatments because Nordstedt provides sufficient suggestion. However, one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine,* 5 USPQ2d 1596, 1600 (Fed. Cir. 1988); *see also* M.P.E.P. § 2141(II)(c). This rule was recently emphasized by the Supreme Court: "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." *KSR* at page 17. In addition, "[i]t is impermissible within the framework of section 103 to pick and choose from one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Hedges,* 228 USPQ 685, 687 (Fed. Cir. 1986).

Here, WO 95/08999 (cited as cite no. 531 in the IDS submitted August 1, 2005) reports that contrary to Nordstedt that an Aβ16-20 peptide was not effective in an animal model of Alzheimer's (see Results, second paragraph). Table XVI of Schenk, US2009/019123 provides data that that antibodies binding to N-terminal epitopes were particularly effective. Barrow, J. Mol. Biol. 225, 1075-1093 (1992) (cited as cite no. 228 in the IDS submitted August 1, 2005) teaches that determinant for Aβ aggregation lies at the C-terminus (Abstract, paragraph

3 and p. 1088, second column, second paragraph). To view Nordstedt in isolation confers a different teaching than to consider it together with other available art as would the skilled person at the relevant time. Viewing the art as a whole, a skilled person could not have confidentially said that residues 16-23 as claimed, had particular significance for treatment of Alzheimer's disease.

The Examiner regards Selkoe's reference to Aβ fragment of 8 or more amino acids as being potential immunogens as strong motivation for using immunogens with as few as eight amino acids. However, as was pointed out previously, Selkoe indicates a preference for amyloid deposits or longer peptides. Although Schenk mentions using peptides with as few as 6 or 8 amino acids, Schenk also teaches using peptides of 3 contiguous amino acids from Aβ (see paragraph 75 of US2009/019123). Again viewing the art as a whole, rather than an individual sentence from Selkoe in isolation, there was no preference for peptides of eight amino, much less a teaching toward the specific eight amino acids represented by Aβ16-23.

Furthermore, an Aβ16-23 conjugate is associated with advantageous properties as further detailed in the attached declaration. The results demonstrate that Aβ16-23 is useful in inhibiting cognitive deficits when administered to young mice (i.e. prophylaxis) or improving contextual memory in older mice (i.e. treatment) (see Declaration at paragraphs 4-18). Further, immunization of young pre-plaque bearing mice with Aβ16-23 significantly reduced amyloid plaque formation (see Declaration at paragraphs 19-22). The claimed Aβ16-23 fragment also has the advantage that it does not induce a T-cell response against Aβ above background (see Declaration at paragraphs 23-26). Finally, the declaration shows that that antibodies induced by administration of Aβ16-23 bind to soluble Aβ monomers as well as to soluble higher-order oligomeric Aβ species (see Declaration at paragraphs 27-31), which have been reported to be a toxic form of Aβ.

The present claims are directed to an Aβ16-23 fragment linked to a carrier that helps elicit an immune response for treatment or prophylaxis of Alzheimer's disease. Induced antibodies specifically bind to soluble Aβ in the patient thereby inhibiting formation of amyloid deposits of Aβ in the brain from the soluble Aβ (specification at paragraph 33). The 16-23 fragment is sufficiently long to consistently generate an antibody response (specification at

paragraph 35) with affinity for oligomeric Aβ and have both prophylactic and therapeutic activity in inhibiting cognitive decline, and inhibit plaque formation but is sufficiently short so as to avoid inducing a T-cell response above background against Aβ notwithstanding that it occurs in a region of Aβ (residues 14-30) in which most T-cell epitopes are located (specification at paragraph 0034), as shown by the declaration of Dr. Jack Steven Jacobsen, paragraphs 24 and 25 (copy attached[1]). Lack of a T-cell response against Aβ is advantageous in avoiding side effects occurring in an earlier clinical trial of full-length Aβ (specification at paragraph 0034).

In sum, the additional amino acids in Aβ16-23 relative to Nordstedt's peptide may well contribute to the consistency and nature of the antibody response induced by Aβ16-23 that give rise to its advantageous properties. However, having still further amino acids is potentially disadvantages because it increases the likelihood of a T-cell response against Aβ. The cited art viewed in the aggregate does not teach modification of Nordstedt's peptide so that it has precisely 8 amino acids, much less the specific 8 amino acids represent by Aβ16-23.

Because the asserted case of obviousness changes the principle of operation of Nordstedt and would have rendered Nordsted's peptide unsuitable for its intended purpose, and in any event does not teach the specific peptide claimed or its several properties advantages for prophylactic and therapeutic treatment without inducing a T-cell response against Aβ, withdrawal of the rejection is respectfully requested.

[1] Applicants submit an unexecuted declaration herewith and will provide an executed declaration.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (650) 838-2000.

Respectfully submitted,

/Rosemarie L. Celli/

Rosemarie L. Celli
Reg. No. 42,397

Customer No. 00826
Alston & Bird LLP
Bank of America Plaza
101 South Tryon Sreet, Suite 4000
Charlotte, NC 28280-4000
Tel. Silicon Valley Office (650) 838-2000
Fax Charlotte Office (704) 444-1111

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